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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,071	02/13/2002	David Bar-Or	4172-3-2	8825

22442 7590 09/30/2005

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EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/076,071	**Applicant(s)** BAR-OR ET AL.	
	Examiner Anand U. Desai, Ph.D.	**Art Unit** 1653	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 35 U.S.C. 112, 2nd, 112, 1st written description, and 103.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *531-576*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

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DETAILED ACTION

1. This office action is in response to Amendment filed on September 7, 2005. Claims 531-576 are currently pending and are under examination.

Information Disclosure Statement

2. The information disclosure statement filed on August 29, 2005 and September 12, 2005 fails to comply with 37 CFR 1.97(d) because it lacks a statement as specified in 37 CFR 1.97(e). It has been placed in the application file, but the information referred to therein has not been considered.

Withdrawal of Rejections

3. The rejection of claims 561, 562, and 569-576 under 35 U.S.C. 112, 2nd paragraph is withdrawn.

4. The rejection of claims 531-576 under 35 U.S.C. 112, 1st paragraph, as failing to comply with the written description requirement is withdrawn.

5. The rejection of claims 531-576 under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (Neurosurgery 37(2): 287-293 (1995)) in view of Harford and Sarkar (Acc. Chem. Res. 30: 123-130 (1997)) is withdrawn.

Maintenance of Objections and Rejections

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 41, line 10. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 531-576 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an angiogenic disease or condition by inhibiting angiogenesis using a metal-binding peptide disclosed as L-Asp-L-Ala-L-His-L-Lys, does not reasonably provide enablement for a method of treating an angiogenic disease or condition with a metal-binding peptide encompassed by the formula, P_1-P_2; P_1 is Xaa_1 Xaa_2 His or Xaa_1 Xaa_2 His Xaa_3, the P_1 portion of the peptide is linear, P_2 is $(Xaa_4)_n$, where n is 0-100, and Xaa_1, Xaa_2, Xaa_3, and Xaa_4 are amino acids disclosed in claim 531. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn to a method of treating an angiogenic disease or condition in an animal comprising administering to the animal an effective amount of a metal-binding peptide, where the peptide sequence is encompassed by the formula P_1-P_2; P_1 is Xaa_1 Xaa_2 His or Xaa_1 Xaa_2 His Xaa_3, the P_1 portion of the peptide is linear, P_2 is $(Xaa_4)_n$, where n is 0-100, and wherein in the identifiers Xaa_1, Xaa_2, Xaa_3, and Xaa_4 are amino acids disclosed in claim 531.

2.) The breadth of the claims: the claims are extremely broad in that a very large number of peptides could be encompassed by formula for the metal-binding peptide.

3.) The predictability or unpredictability of the art: there is unpredictability in the art with regard to inhibiting angiogenesis using metal chelating agents (See Applicants Remarks dated September 7, 2005, page 14 of 19, 1st indented paragraph, last sentence, "...Applicants submit that there was not sufficient predictability in the art of inhibiting angiogenesis using metal chelating agents at the time of filing of the application using metal chelating agents to render obvious the presently claimed invention in view of Yoshida.") Furthermore, experiments have shown that copper-binding peptides can **stimulate** angiogenesis; Lane, T. et al have shown that SPARC, and a peptide sequence within SPARC, particularly, L-Lys-L-Gly-L-His-L-Lys, stimulates angiogenesis (see Lane, T. et al. Journal of Cell Biology, 125(4): 929-943 (1994), particularly Results, page 932-935, SPARC and Peptides Derived from SPARC 113-130 Stimulate the Formation of Endothelial Cords In Vitro, and SPARC 113-130 and KGHK Specifically Stimulate Angiogenesis In Vivo sections, Figures 3, and 4, and page 931, Table 1). Thus, due to the unpredictability of metal-binding peptides affect on angiogenesis, both inhibitory and stimulatory, there is no way to predict whether all of the metal-binding peptides encompassed by the formula of claim 531 will treat an angiogenic disease or conditions by inhibiting angiogenesis.

4.) & 5.) The amount of direction or guidance presented:/The presence or absence of working examples: the specification provides guidance with respect to the metal-binding peptide, L-Asp-L-Ala-L-His-L-Lys, ability to inhibit angiogenesis in the chorioallantoic membranes of fertilized eggs as discussed in example 12, but provides no guidance whatsoever in selecting

other peptides that might have the needed conformations to bind metal ions and inhibit angiogenesis. Further, no guidance is provided as to how to determine which peptides can be administered to an animal to treat an angiogenic disease or condition, wherein the angiogenic disease or condition is a neoplastic disease, a connective tissue disorder, psoriasis, an ocular angiogenic disease, a cardiovascular disease, a cerebral vascular disease, hemophiliac joints, an immune disorder, a benign tumor, hypertrophy, endometriosis, polyposis, or obesity.

6.) The quantity of experimentation necessary: there is a large quantity of experimentation necessary to determine which peptides are capable of inhibiting angiogenesis and treating the scope of angiogenic disease or condition currently being claimed.

7.) The state of the prior art: the prior art has shown that "antiangiogenic treatment shows efficacy in animal tumor models" and "that copper is required for angiogenesis" (see Brewer, G. et al. Clinical Cancer Research, Vol. 6, pp. 1-10 Jan. (2000), particularly Introduction). However, Brewer, G. et al. also state that certain patients with very rapidly progressive large tumors may be relatively poor candidates for this approach to antiangiogenesis therapy as a single modality, because of the ability of tumors to sequester cooper (see page 7, 3rd paragraph of Discussion).

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 531, 532, 534-536, 541, 543-545, and 569 are rejected under 35 U.S.C. 102(b) as being anticipated by Lane, T. et al. (Journal of Cell Biology, 125(4): 929-943 (1994)).

11. Lane, T. et al. disclose the stimulation of angiogenesis in bovine aortic endothelial cultured cells and chorioallantoic membrane angiogenesis assays upon administration of a copper-binding peptide. The peptide sequence is L-Lys-L-Gly-L-His-L-Lys. A method of treating an angiogenic disease or condition can reasonably encompass the stimulation of new blood vessels, such as during treating a cardiovascular condition. Therefore Lang, T. et al. discloses a method of treating an angiogenic disease or condition comprising administering the copper-binding peptide, L-Lys-L-Gly-L-His-L-Lys (current application, claims 531, 532, 534-536, 541, 543-545, and 569).

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 26, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER